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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09-891,023	06/25/2001	Damir Janigro	26336-8	9460

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EXAMINER

NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
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1647

8

DATE MAILED: 02/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/891,023

Applicant(s)

JANIGRO ET AL.

Examiner

Christopher Nichols, Ph.D.

Art Unit

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 October 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above claim(s) 8-20 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 June 2001 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other _____

DETAILED ACTION

Election/Restrictions

1. Applicant's election with **traverse** of Group I (claims 1-7) drawn to a method of diagnosis of blood brain permeability in Paper No. 7 (26 October 2002) is acknowledged. The traversal is on the ground(s) that searches of Groups I, II, and III would be co-extensive and thus do not represent a search burden. This is not found persuasive because Group I is drawn to a method of diagnosis, Group II is directed to a method for treating a patient, and Group III is drawn to a method of diagnosing cancer. All three Groups represent distinct and independent inventions the search and examination of which is not co-extensive and represents a search burden. Claims 8-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. The requirement is still deemed proper and is therefore made FINAL.

Status of Application, Amendments, and/or Claims

2. Claims 1-7 are under examination and claims 8-20 are withdrawn from consideration as discussed above.
3. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647, Examiner Christopher Nichols.

Drawings

4. The drawings are objected to because each sheet must include a top margin of at least 2.5 cm. (1 inch), a left side margin of at least 2.5 cm. (1 inch), a right side margin of at least 1.5 cm. (5/8 inch), and a bottom margin of at least 1.0 cm. (3/8 inch), thereby leaving a sight no greater than 17.0 cm. by 26.2 cm. on 21.0 cm. by 29.7 cm. (DIN size A4) drawing sheets, and a sight no greater than 17.6 cm. by 24.4 cm. (6 15/16 by 9 5/8 inches) on 21.6 cm. by 27.9 cm. (8 1/2 by 11 inch) drawing sheets. Proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Specification

5. The abstract of the disclosure is objected to because it is too long. Correction is required. See MPEP § 608.01(b).

Applicant is reminded of the proper language and format for an abstract of the disclosure. The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details. The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Westaby et al. [(1996) "Serum S100 Protein: A Potential Marker for Cerebral Events During Cardiopulmonary Bypass." Ann. Thorac. Surg. 61: 88-92 (**IDS #BG**)]. Westaby et al. (1996) discloses a method of measuring S100 β in human blood samples via form of immunoprecipitation thus meeting the limitations of claims 1, 3, and 4 (pp. 89 "The Assay"). Westaby et al. (1996) also teaches that elevated S100 β levels in blood is indicative of increased blood brain barrier (BBB) permeability and neuronal damage thus meeting the limitations of claim 1 (pp. 88). Westaby et al. (1996) also teaches statistical analysis of S100 β μ g/L as a measure of cardiopulmonary distress (due to surgery) thus meeting the limitations of claim 2 (Figure 1). Also, Westaby et al. (1996) discusses the use of S100 β as an effective indicator for quantifying the extent of injury following a stroke wherein S100 β levels correlate with cerebral infarct size thus meeting the limitations of claim 5 (pp. 91). Westaby et al. (1996) also suggests the use of S100 β levels as an indicator of increased BBB permeability over the course of recovering from cardiopulmonary bypass surgery thus meeting the limitations of claim 6 (pp. 90).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Westaby et al. [(1996) "Serum S100 Protein: A Potential Marker for Cerebral Events During Cardiopulmonary Bypass." Ann. Thorac. Surg. 61: 88-92 (**IDS #BG**)] taken with Herrmann et al. [(2000) "Release of Glial Tissue-Specific Proteins After Acute Stroke." Stroke 31: 2670-2677] and Strachan et al. (1999) "Evaluation of Serum Markers of Neuronal Damage Following Severe Hypoglycemia in Adults with Insulin-treated Diabetes Mellitus." Diabetes/Metabolism Research and Reviews 15: 9-12 (**IDS #BB**)].
8. Westaby et al. (1996) discloses a method of measuring S100 β in human blood samples via form of immunoprecipitation (pp. 89 "*The Assay*"). Westaby et al. (1996) teaches that elevated S100 β levels in blood is indicative of increased blood brain barrier (BBB) permeability, statistical analysis of S100 β μ g/L as a measure of cardiopulmonary distress (due to surgery), and the use of S100 β as an effective indicator for quantifying the extent of injury following a stroke wherein S100 β levels correlate with cerebral infarct size thus meeting the limitations of claim 7 (pp. 88, pp. 91, Figure 1). Westaby et al. (1996) does not teach, however, the use of a combination of measuring NSE and/or GFAP with S100 β serum levels.
9. Herrmann et al. (2000) teaches the use of an immunoassay to measure GFAP serum levels as an indicator of neuronal distress (pp. 2671-2672 "*Neurobiochemical Analysis*", Figures

1-4). Herrmann et al. (2000) also suggests the use of immunoassay measurement of S100 β and GFAP as useful over the course of recovering from injury to determine brain lesion size, neurological status, and the outcome of recovery of patients thus meeting the limitations of claims 5, 6, and 7 (pp. 2674-2676 “**Discussion**”). Herrmann et al. (2000) mentions but does not teach, however, the use of detecting neuronal-specific enolase (NSE) as a measure of neuronal distress/injury.

10. Strachan et al. (1999) teaches a method of determining NSE and S100 β levels in serum using an immunoprecipitation assay (pp. 7 “**Measurements of serum NSE and S-100 concentrations**”, Figures 3-5). Strachan et al. (1999) teaches the determination of NSE and S100 β levels in serum as part of an analysis of the stages of Type 1 diabetes and evaluation of treatment regimens thus meeting the limitations of claims 5, 6, and 7 (pp. 7 “**Statistical analyses**”, pp. 7-8 “**Case histories**”).

11. Thus, it would have been obvious to a person of ordinary skill in the art at the time of the invention to combine an immunoassay measurement of serum S100 β levels as taught by Westaby et al. (1996) with an immunoassay measurement of serum GFAP as taught by Herrmann et al. (2000) and/or NSE levels as taught by Strachan et al. (1999) as a method of diagnosing blood brain barrier permeability based on the S100 β levels and signs of neuronal distress as determined by the serum NSE and/or GFAP levels [Westaby et al. (1996) pp. 90-91; Herrmann et al. (2000) pp. 2670 “**Conclusions**”, pp. 2674-2676 “**Discussion**”; Strachan et al. (1999) pp. 5 “**Conclusions**”, pp. 6, pp. 10-11 “**Discussion**”].

12. A person of ordinary skill in the art at the time of the invention would have been motivated to make these modifications because the standard method of measuring S100 β

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involved a spinal tap, a painful and difficult procedure. In addition, by measuring serum levels of the respective proteins, multiple measurements could be made more efficiently and with less discomfort to the patient over the course of a disease and/or corresponding therapy [Westaby et al. (1996) pp. 90-91; Herrmann et al. (2000) pp. 2670 "**Conclusions**", pp. 2674-2676

"**Discussion**"; Strachan et al. (1999) pp. 5 "**Conclusions**", pp. 6, pp. 10-11 "**Discussion**"].

13. A person of ordinary skill in the art at the time of the invention would have a reasonable expectation of success in making the above mentioned modifications because GFAP, and NSE were known to be associated with neuronal distress/injury and S100 β was known to be associated with blood brain barrier permeability. Furthermore, S100 β , GFAP, and NSE were all successfully measured in human blood samples via an immunoassay at the time of the invention [Westaby et al. (1996) pp. 90-91; Herrmann et al. (2000) pp. 2670 "**Conclusions**", pp. 2674-2676 "**Discussion**"; Strachan et al. (1999) pp. 5 "**Conclusions**", pp. 6, pp. 10-11 "**Discussion**"].

14. Thus the invention as a whole was *prima facie* obvious over the prior art.

Summary

15. Claims 1-7 are hereby rejected.

16. Art cited as of interest, concerning immunoprecipitation, that accurate immunoassays were available at the time of the invention with which to detect S100 β levels in serum. See Missler et al. [(1 July 2000) "Validation and Comparison of Two Solid-Phase Immunoassays for the Quantification of S100 β in Human Blood." Clinical Chemistry 46(7): 993-996] and Takahashi et al. [(1 August 1999) "Rapid and Sensitive Immunoassay for the Measurement of Serum S100 β Using Isoform-specific Monoclonal Antibody." Clinical Chemistry 45(8): 1307-1311].

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher J. Nichols whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

CJN
January 31, 2003

Elizabeth C. Hermine